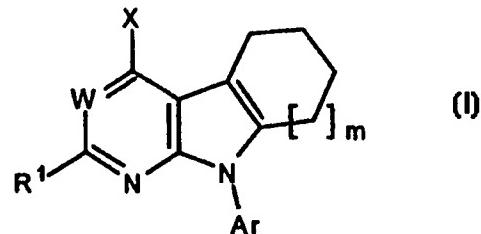




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(54) Title: AMINOALKYL SUBSTITUTED 5,6,7,8-TETRAHYDRO-9H PYRIMIDINO[2,3-B]INDOLE AND 5,6,7,8-TETRAHYDRO-9H-PYRIMIDINO[4,5-B]INDOLE DERIVATIVES: CRF1 SPECIFIC LIGANDS



(57) Abstract

Disclosed are compounds of formula (I), wherein Ar, R¹, W, X and m are substituents as defined herein. These compounds are modulators of CRF receptors and are therefore useful for treating affective disorder, anxiety, depression, headache, irritable bowel syndrome post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound of Formula (I).

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Aminoalkyl Substituted 5,6,7,8-Tetrahydro-9H-Pyridino[2,3-b]indole and 5,6,7,8-Tetrahydro-9H-Pyrimidino[4,5-b]indole Derivatives: CRF1 Specific Ligands

5

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to aminoalkyl substituted 5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole and 5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole derivatives, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders, neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

15

Description of the Related Art

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Nat. Acad. Sci. (USA) 80:4851 (1983); W. Vale et al., Science 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G.F. Koob, Persp. Behav. Med. 2:39 (1985); E.B. De Souza et al., J. Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, Physiological Reviews 69:1 (1989); J.E. Morley, Life Sci. 41:527 (1987)].

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Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and 5 pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

10

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989). Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, 15 there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147(1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that 20 tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated 5 in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist 10 produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and 15 benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in 20 the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist Ro 15-1788, which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the 25 benzodiazepine inverse agonist FG 7142 enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

It has been further postulated that CRF has a role in immunological, cardiovascular or heart-related diseases such as 30 hypertension, tachycardia and congestive heart failure, stroke and osteoporosis. CRF has also been implicated in premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress.

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized 5 however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α -helical CRF₉₋₄₁) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E. B. De Souza and C .B Nemeroff eds., CRC Press p221 (1990)].

15

SUMMARY OF THE INVENTION

In one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in mammals. In another aspect, the present invention provides novel compounds of Formula I (described below) which are useful as antagonists of corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and suppress CRF hypersecretion. The present invention also provides pharmaceutical compositions containing such compounds of Formula I, and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect, the present invention provides novel compounds, pharmaceutical compositions and methods for the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies;

generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including 5 major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative 10 diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ileus and colonic hypersensitivity associated by psychopathological disturbances or stress; 15 eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADR); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., 20 cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress 25 induced fevers in humans and the following animal diseases: porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; 30 urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and

alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals.

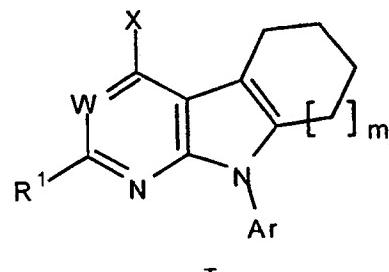
Such methods involve administration to a mammal of a therapeutically effective amount of a compound of Formula I.

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In yet another aspect of the invention, the compounds provided the invention (and especially radio-labeled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind 10 to the CRF receptor.

The compounds encompassed by the instant invention and represented by general Formula I:

15



wherein:

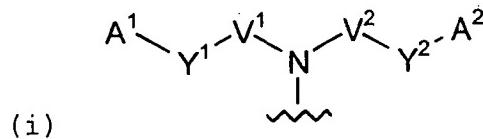
Ar is phenyl, 1- or 2-naphthyl, 2-, 3-, or 4-pyridyl, 2-, 4- or 20 5-pyrimidinyl, optionally mono-, di-, or tri-substituted with halogen, trifluoromethyl, hydroxy, amino, carboxamido, C₁-C₆ alkyl, C₁-C₆ alkoxy, with the proviso that at least one of the positions ortho or para to the point of attachment of Ar to the tricyclic ring system is 25 substituted;

R¹ is hydrogen, halogen, trifluoromethyl, C₁-C₆ alkyl, or (C₁-C₆ alkyl)-G¹-R² where G¹ is oxygen or sulfur and R² is hydrogen or C₁-C₆ alkyl;

W is N or C-R³ where R³ is hydrogen or C₁-C₆ alkyl;

m is 0, 1, or 2;

X is

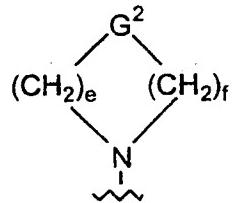


5 wherein

V¹ and V² are CH₂, CO, CS, SO₂ or CH(C₁-C₆ alkyl), with the proviso that both V¹ and V² cannot both be CO, CS or SO₂;

10 Y¹ and Y² independently represent a bond or C₁-C₆ alkylene;

A¹ is NR⁴R⁵ wherein R⁴ and R⁵ are independently hydrogen or a C₁-C₆ alkyl group which and optionally forms a heterocycloalkyl group with Y¹; acetyl or sulfonyl with the proviso that R⁴ and R⁵ cannot both be acetyl or sulfonyl; or 15 NR⁴R⁵ taken together form a C₃-C₆ heterocycloalkyl or a group of the formula:



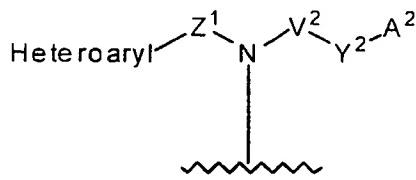
20 wherein e and f are independently 1, 2, or 3 and the sum of e and f is at least 3; and

G² is

NR⁶ wherein R⁶ is hydrogen or C₁-C₆ alkyl, or

$\text{CH}(\text{C}_0\text{-C}_6 \text{ alkylene})\text{-G}^3\text{-R}^7$ wherein G^3 is CONH ,
 $\text{CONH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, NH , $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ and R^7
is hydrogen or $\text{C}_1\text{-C}_6$ alkyl; or
 CONH_2 , $\text{CO}[\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{R}^8]$ wherein R^8 is
5 hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

A^2 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-G}^4\text{-R}^9$
wherein G^4 is oxygen or sulfur and R^9 is hydrogen,
trifluoromethyl or $\text{C}_1\text{-C}_6$ alkyl;

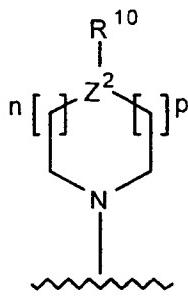


10 (iii)

wherein heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-pyrazinyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally mono- or disubstituted with halogen, trifluoromethyl, amino, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, with the proviso that tetrazolyl can have at most one substituent;

15 Z^1 is $\text{C}_1\text{-C}_6$ alkyl; and

20 V^2 , Y^2 and A^2 are as defined above;



(iii)

wherein

Z^2 is carbon or nitrogen;

where

when Z^2 is CH, n is 0, 1, 2 or 3 and p is 1, 2, or 3,

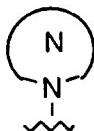
R^{10} is carboxamido, or $(C_1-C_6\text{ alkylene})^5-G^5-R^{11}$

5 wherein G^5 is NH, $NH(C_1-C_6\text{ alkyl})$ and R^{11} is hydrogen or $C_1-C_6\text{ alkyl}$;

when Z^2 is carbon, n is 1 or 2 and p is 1 or 2, R^{10} is amino; or

when Z^2 is nitrogen, n is 1 or 2 and p is 1 or 2, R^{10} is 10 hydrogen; or

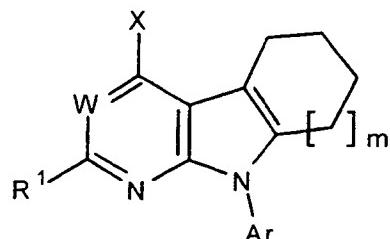
(iv) a nitrogen heterocycle of the formula:



wherein the N-ring represents triazolyl, tetrazolyl, imidazolyl, or pyrazolyl, each of which is 15 optionally substituted with amino, trifluoromethyl, carboxamido, or $(C_1-C_6\text{ alkylene})^6-G^6-R^{12}$ wherein G^6 is NH, $NH(C_1-C_6\text{ alkyl})$ and R^{12} is hydrogen or $C_1-C_6\text{ alkyl}$.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the invention provides compounds of Formula I:



5

I

wherein:

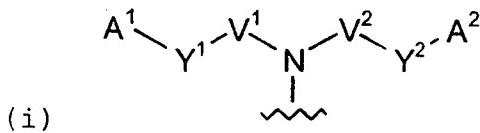
Ar is phenyl, 1- or 2-naphthyl, 2-, 3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, optionally mono-, di-, or tri-substituted
10 with halogen, trifluoromethyl, hydroxy, amino, carboxamido, C₁-C₆ alkyl, C₁-C₆ alkoxy, with the proviso that at least one of the positions ortho or para to the point of attachment of Ar to the tricyclic ring system is substituted;

15 R¹ is hydrogen, halogen, trifluoromethyl, C₁-C₆ alkyl, or (C₁-C₆ alkyl)-G¹-R² where G¹ is oxygen or sulfur and R² is hydrogen or C₁-C₆ alkyl;

W is N or C-R³ where R³ is hydrogen or C₁-C₆ alkyl;

m is 0, 1, or 2;

20 X is



wherein

V¹ and V² are CH₂, CO, CS, SO₂ or CH(C₁-C₆ alkyl), with the proviso that both V¹ and V² cannot both be CO, CS or SO₂;
25

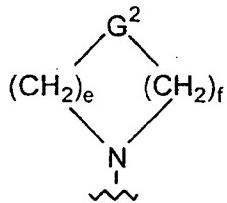
Y^1 and Y^2 independently represent a bond or C₁-C₆ alkylene;

A^1 is NR⁴R⁵ wherein R⁴ and R⁵ are independently hydrogen or a C₁-C₆ alkyl group which and optionally

5 forms a heterocycloalkyl group with Y^1 ;

acetyl or sulfonyl with the proviso that R⁴ and R⁵ cannot both be acetyl or sulfonyl; or

NR⁴R⁵ taken together form a C₃-C₆ heterocycloalkyl or a group of the formula:



10

wherein e and f are independently 1, 2, or 3 and the sum of e and f is at least 3; and

G^2 is

NR⁶ wherein R⁶ is hydrogen or C₁-C₆ alkyl, or

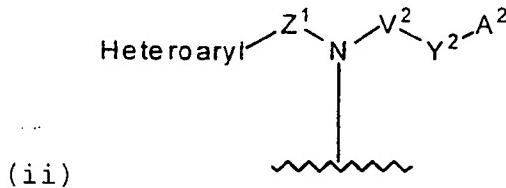
15 CH(C₀-C₆ alkylene)-G³-R⁷ wherein G³ is CONH,

CONH(C₁-C₆ alkyl), NH, NH(C₁-C₆ alkyl) and R⁷ is hydrogen or C₁-C₆ alkyl; or

CONH₂, CO[N(C₁-C₆ alkyl)R⁸] wherein R⁸ is hydrogen or C₁-C₆ alkyl;

20 A^2 is hydrogen, C₁-C₆ alkyl, (C₁-C₆ alkylene)-G⁴-R⁹

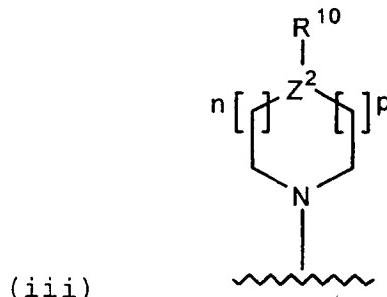
wherein G⁴ is oxygen or sulfur and R⁹ is hydrogen, trifluoromethyl or C₁-C₆ alkyl;



wherein heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-pyrazinyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally mono- or disubstituted with halogen, trifluoromethyl, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, with the proviso that tetrazolyl can have at most one substituent;

10. Z¹ is C₁-C₆ alkyl; and

V², Y² and A² are as defined above;



wherein

Z² is carbon or nitrogen;

15. wherein

when Z² is CH, n is 0, 1, 2 or 3 and p is 1, 2, or 3,

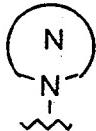
R¹⁰ is carboxamido, or (C₁-C₆ alkylene)-G⁵-R¹¹

wherein G⁵ is NH, NH(C₁-C₆ alkyl) and R¹¹ is hydrogen or C₁-C₆ alkyl;

20. when Z² is carbon, n is 1 or 2 and p is 1 or 2, R¹⁰ is amino; or

when Z^2 is nitrogen, n is 1 or 2 and p is 1 or 2, R^{10} is hydrogen; or

(iv) a nitrogen heterocycle of the formula:



5 wherein the N-ring represents triazolyl, tetrazolyl, imidazolyl, or pyrazolyl, each of which is optionally substituted with amino, trifluoromethyl, carboxamido, or (C_1-C_6 alkylene) 6 - R^{12} where G^6 is NH, $NH(C_1-C_6$ alkyl) and R^{12} is hydrogen or C_1-C_6 alkyl.

Preferred compounds of Formula I are those where V^1 and V^2 represent methylene; Y^1 is a bond; A^1 represents pyrrolidinyl, morpholinyl, piperazinyl, or mono- or di- C_1-C_6 alkyl; Y^2 represents a bond or methylene; and A^2 represents C_1-C_6 alkyl or C_1-C_6 alkoxy methyl.

Other preferred compounds of Formula I are those where each R_a independently represents C_1-C_6 alkyl; and A^2 is C_1-C_6 cycloalkyl. In other preferred compounds of I, A^2 is (C_3-C_5) cycloalkyl (C_1-C_4) alkyl.

Still other preferred compounds of I include are those where

A^1 is

25 NR^4R^5 where R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl; or

NR^4R^5 forms a 5 or 6-membered nitrogen heterocycle optionally containing an oxygen or second nitrogen atom;

Y^1 is C_1-C_6 alkylene;

30 Y^2 is a bond or C_1-C_6 alkylene;

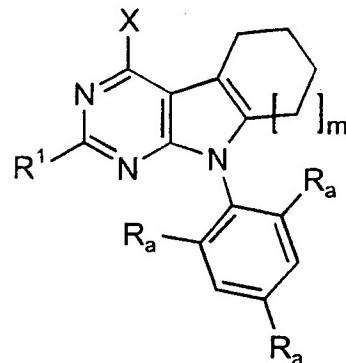
V^1 is methylene; and V^2 is methylene.

More preferably, A^2 is (C_3 - C_5)cycloalkyl. Still more preferably, R^4 and R^5 are independently C_1 - C_6 alkyl. Other particularly preferred compounds of Formula I are those where each R_a is methyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1 - C_3 alkyl.

In yet other preferred compounds of Formula I, m is 1 or 2, more preferably 1. In still other preferred compounds of I, m is 1 and R^1 is C_1 - C_3 alkyl, more preferably methyl.

10

Preferred compounds of the invention have Formula II:



II

wherein:

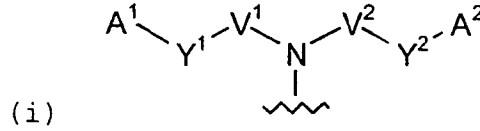
15 each R_a independently represents C_1 - C_6 alkyl;

R^1 is hydrogen, halogen, trifluoromethyl, C_1 - C_6 alkyl, or (C_1 - C_6 alkyl)- G^1 - R^2 where G^1 is oxygen or sulfur and R^2 is hydrogen or C_1 - C_6 alkyl;

W is N or $C-R^3$ where R^3 is hydrogen or C_1 - C_6 alkyl;

20 m is 0, 1, or 2;

X is

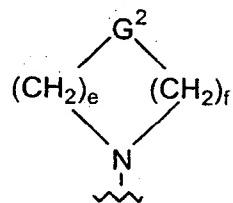


wherein

V^1 and V^2 are CH_2 , CO , CS , SO_2 or $CH(C_1-C_6 \text{ alkyl})$, with the proviso that both V^1 and V^2 cannot both be CO , CS or SO_2 ;

5 Y^1 and Y^2 independently represent a bond or C_1-C_6 alkylene;

A¹ is NR^4R^5 wherein R^4 and R^5 are independently hydrogen or a C_1-C_6 alkyl group which and optionally forms a heterocycloalkyl group with Y^1 ; acetyl or sulfonyl with the proviso that R^4 and R^5 cannot both be acetyl or sulfonyl; or
10 NR^4R^5 taken together form a C_3-C_6 heterocycloalkyl or a group of the formula:



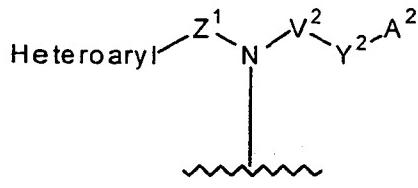
15 wherein e and f are independently 1, 2, or 3 and the sum of e and f is at least 3; and

G^2 is

NR^6 wherein R^6 is hydrogen or C_1-C_6 alkyl, or
20 $CH(C_0-C_6 \text{ alkylene})-G^3-R^7$ wherein G^3 is $CONH$, $CONH(C_1-C_6 \text{ alkyl})$, NH , $NH(C_1-C_6 \text{ alkyl})$ and R^7 is hydrogen or C_1-C_6 alkyl; or

$CONH_2$, $CO[N(C_1-C_6 \text{ alkyl})R^8]$ wherein R^8 is hydrogen or C_1-C_6 alkyl;

A^2 is hydrogen, C_1-C_6 alkyl, $(C_1-C_6$ alkylene)- G^4 - R^9
 wherein G^4 is oxygen or sulfur and R^9 is hydrogen,
 trifluoromethyl or C_1-C_6 alkyl;

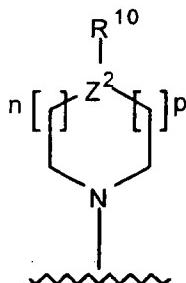


5 (ii)

wherein heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-pyrazinyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally mono- or disubstituted with halogen, trifluoromethyl, amino, C_1-C_6 alkyl, C_1-C_6 alkoxy, with the proviso that tetrazolyl can have at most one substituent;

10 Z^1 is C_1-C_6 alkyl; and

15 V^2 , Y^2 and A^2 are as defined above;



(iii)

wherein

Z^2 is carbon or nitrogen;

wherein

20 when Z^2 is CH, n is 0, 1, 2 or 3 and p is 1, 2, or 3,

R^{10} is carboxamido, or $(C_1-C_6$ alkylene)- G^5 - R^{11}

wherein G^5 is NH, NH(C₁-C₆ alkyl) and R¹¹ is hydrogen or C₁-C₆ alkyl;

when Z² is carbon, n is 1 or 2 and p is 1 or 2, R¹⁰ is amino; or

5 when Z² is nitrogen, n is 1 or 2 and p is 1 or 2, R¹⁰ is hydrogen; or

(iv) a nitrogen heterocycle of the formula:



10 wherein the N-ring represents triazolyl, tetrazolyl, imidazolyl, or pyrazolyl, each of which is optionally substituted with amino, trifluoromethyl, carboxamido, or (C₁-C₆ alkylene)-G⁶-R¹² wherein G⁶ is NH, NH(C₁-C₆ alkyl) and R¹² is hydrogen or C₁-C₆ alkyl.

15 Preferred compounds of Formula II are those where V¹ and V² represent methylene; Y¹ is a bond; A¹ represents pyrrolidinyl, morpholinyl, piperazinyl, or mono- or di-C₁-C₆ alkyl; Y² represents a bond or methylene; and A² represents C₁-C₆ alkyl or C₁-C₆ alkoxyethyl.

20 Other preferred compounds of Formula II are those where each R_a independently represents C₁-C₆ alkyl; A² is (C₃-C₅)cycloalkyl(C₁-C₄)alkyl or (C₃-C₅)cycloalkyl; A¹ is

25 NR⁴R⁵ where R⁴ and R⁵ are independently hydrogen, C₁-C₆ alkyl; or

NR⁴R⁵ forms a 5 or 6-membered nitrogen heterocycle optionally containing an oxygen or second nitrogen atom;

Y¹ is C₁-C₆ alkylene;

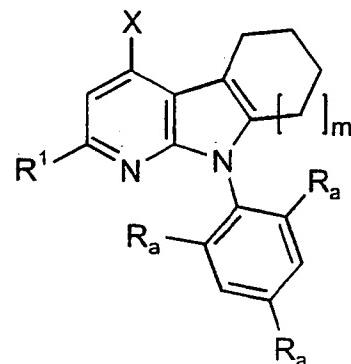
30 Y² is a bond or C₁-C₆ alkylene;

V¹ is methylene; and V² is methylene.

More preferably, A² is cyclopropyl(C₁-C₃)alkyl or (C₃-C₅)cycloalkyl; and R⁴ and R⁵ are independently C₁-C₆ alkyl. Particularly preferred compounds of Formula II include those where A² is (C₃-C₅)cycloalkyl; Y² is a bond; and R⁴ and R⁵ are the same and represent C₁-C₃ alkyl. Other particularly preferred compounds of Formula II are those where each R_a is methyl; A² is cyclopropyl; Y² is a bond; and R⁴ and R⁵ are the same and represent C₁-C₃ alkyl.

In preferred compounds of Formula II, m is 1 or 2, more preferably 1. In other preferred compounds of II, m is 1 and R¹ is C₁-C₃ alkyl, more preferably methyl.

Other preferred compounds of the invention have Formula III:



III

wherein:

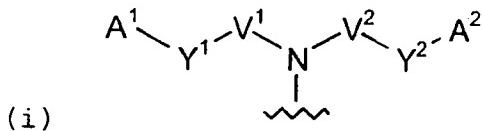
each R_a independently represents C₁-C₆ alkyl;

R¹ is hydrogen, halogen, trifluoromethyl, C₁-C₆ alkyl, or (C₁-C₆ alkyl)-G¹-R² where G¹ is oxygen or sulfur and R² is hydrogen or C₁-C₆ alkyl;

W is N or C-R³ where R³ is hydrogen or C₁-C₆ alkyl;

m is 0, 1, or 2;

X is



wherein

V^1 and V^2 are CH_2 , CO , CS , SO_2 or $CH(C_1-C_6$ alkyl), with
the proviso that both V^1 and V^2 cannot both be CO , CS
5 or SO_2 ;

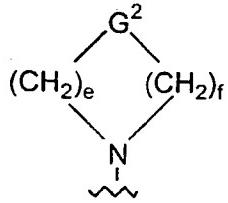
Y^1 and Y^2 independently represent a bond or C_1-C_6 alkylene;

A^1 is NR^4R^5 wherein R^4 and R^5 are independently hydrogen or a C_1-C_6 alkyl group which and optionally

10 forms a heterocycloalkyl group with Y^1 ;

acetyl or sulfonyl with the proviso that R^4 and R^5 cannot both be acetyl or sulfonyl; or

NR^4R^5 taken together form a C_3-C_6 heterocycloalkyl or a group of the formula:



15

wherein e and f are independently 1, 2, or 3 and the sum of e and f is at least 3; and

G^2 is

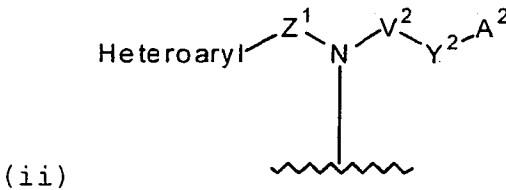
NR^6 wherein R^6 is hydrogen or C_1-C_6 alkyl, or

20 $CH(C_0-C_6$ alkylene)- G^3-R^7 wherein G^3 is $CONH$, $CONH(C_1-C_6$ alkyl), NH , $NH(C_1-C_6$ alkyl) and R^7 is hydrogen or C_1-C_6 alkyl; or

CONH_2 , $\text{CO}[\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{R}^8]$] wherein R^8 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

A^2 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-G}^4\text{-R}^9$ wherein G^4 is oxygen or sulfur and R^9 is hydrogen, trifluoromethyl or $\text{C}_1\text{-C}_6$ alkyl;

5



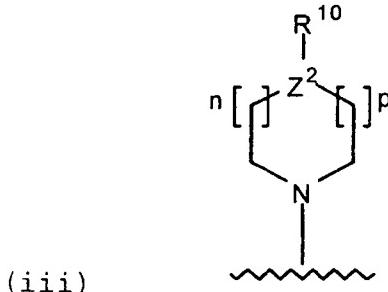
10

15

wherein heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-pyrazinyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally mono- or disubstituted with halogen, trifluoromethyl, amino, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, with the proviso that tetrazolyl can have at most one substituent;

Z^1 is $\text{C}_1\text{-C}_6$ alkyl; and

V^2 , Y^2 and A^2 are as defined above;



wherein

20 Z^2 is carbon or nitrogen;

wherein

when Z^2 is CH, n is 0, 1, 2 or 3 and p is 1, 2, or 3,

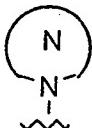
R^{10} is carboxamido, or $(C_1-C_6 \text{ alkylene})^5-G^{11}-R^{11}$

wherein G^5 is NH, NH(C₁-C₆ alkyl) and R^{11} is hydrogen or C₁-C₆ alkyl;

5 when Z^2 is carbon, n is 1 or 2 and p is 1 or 2, R^{10} is amino; or

when Z^2 is nitrogen, n is 1 or 2 and p is 1 or 2, R^{10} is hydrogen; or

(iv) a nitrogen heterocycle of the formula:



10

wherein the N-ring represents triazolyl, tetrazolyl, imidazolyl, or pyrazolyl, each of which is optionally substituted with amino, trifluoromethyl, carboxamido, or $(C_1-C_6 \text{ alkylene})^6-G^{12}-R^{12}$ wherein G^6 is NH, NH(C₁-C₆ alkyl) and R^{12} is hydrogen or C₁-C₆ alkyl.

15

Preferred compounds of Formula III are those where V¹ and V² represent methylene; Y¹ is a bond; A¹ represents pyrrolidinyl, morpholinyl, piperazinyl, or mono- or di-C₁-C₆ alkyl; Y² represents a bond or methylene; and A² represents C₁-C₆ alkyl or C₁-C₆ alkoxyethyl.

Other preferred compounds of Formula III include those where each R_a is independently halogen, trifluoromethyl, hydroxy, amino, C₁-C₆ alkyl, or C₁-C₆ alkoxy. Specific preferred compounds of III are those where at least one R_a is C₁-C₆ alkyl and the other R_a groups are independently C₁-C₆ alkyl, halogen, C₁-C₆ alkoxy or trifluoromethyl.

Other preferred compounds of Formula III are those where each R_a independently represents C₁-C₆ alkyl;

A² is (C₃-C₅)cycloalkyl(C₁-C₄)alkyl or (C₃-C₅)cycloalkyl;

A¹ is

NR⁴R⁵ where R⁴ and R⁵ are independently hydrogen, C₁-C₆ alkyl; or

5 NR⁴R⁵ forms a 5 or 6-membered nitrogen heterocycle optionally containing an oxygen or second nitrogen atom;

Y¹ is C₁-C₆ alkylene;

Y² is a bond or C₁-C₆ alkylene;

10 V¹ is methylene; and V² is methylene.

More preferably, A² is cyclopropyl(C₁-C₃)alkyl or (C₃-C₅)cycloalkyl; and R⁴ and R⁵ are independently C₁-C₆ alkyl.

Particularly preferred compounds of Formula III include those where A² is (C₃-C₅)cycloalkyl; Y² is a bond; and R⁴ and R⁵ are

15 the same and represent C₁-C₃ alkyl. Other particularly preferred compounds of Formula III include those where at least one R_a is methyl; A² is (C₃-C₅)cycloalkyl; Y² is a bond; and R⁴

and R⁵ are the same and represent C₁-C₃ alkyl. Highly preferred compounds of Formula III are those where each R_a is methyl; A²

20 is cyclopropyl; Y² is a bond; and R⁴ and R⁵ are the same and represent C₁-C₃ alkyl.

In preferred compounds of Formula III, m is 1 or 2, more preferably 1. In other preferred compounds of III, m is 1 and R¹ is C₁-C₃ alkyl, more preferably methyl.

25 In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e.,

30 optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the 5 invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic 10 solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, 15 formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH₂)_n-ACOOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

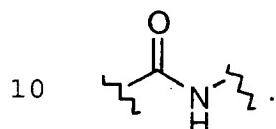
20 The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds 25 encompassed by Formula I.

By "alkyl" or "lower alkyl" in the present invention is meant C₁-C₆ alkyl, i.e., straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, 30 pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred C₁-C₆ alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl or cyclopropylmethyl.

By "C₀-C₆ alkylene" is meant a direct bond or a C₁-C₆ alkylene group.

By "alkoxy" or "lower alkoxy" in the present invention is meant C₁-C₆ alkoxy, i.e., straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexaoxy, and 3-methylpentoxy.

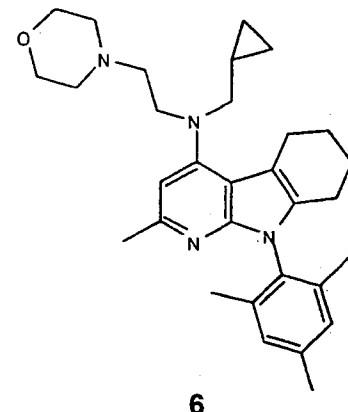
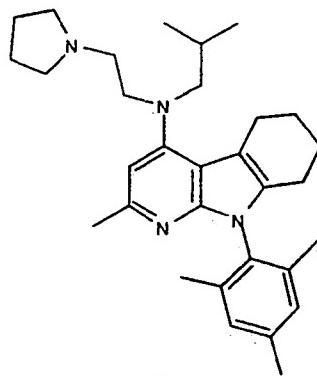
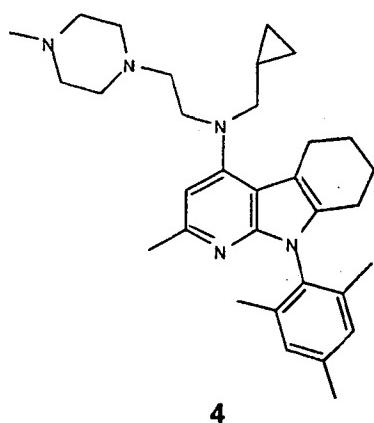
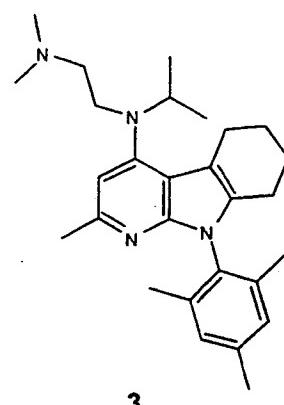
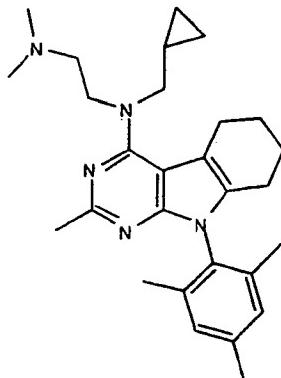
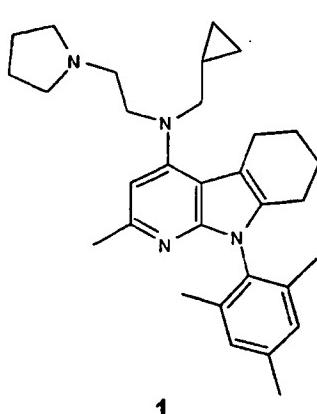
CONH represents an amide functional group, i.e.,



The term "heterocycle" or "heterocycloalkyl" means a monocyclic or bicyclic hydrocarbon group which in which one or more of the ring carbon atoms has been replaced with a heteroatom, e.g., oxygen, sulfur or nitrogen. Such groups preferably have 4 to 10 carbon atoms and 1 to 4 heteroatoms.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

Table 1 shows representative aminoalkyl substituted 5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole and 5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole derivatives of the present invention. The number under each compound is its compound number.

Table 1

The interaction of aminoalkyl substituted 5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole and 5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole derivatives of the invention with CRF receptors is shown in the examples. This interaction results in the pharmacological activities of these compounds as illustrated in relevant animal models.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a

compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the

active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting

Information on patent family members

International Application No
PCT/US 99/07122

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 597 527 A (M. E. FREED) 18 May 1971 see claims 1,2 -----	1-56

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D471/04 A61K31/40 A61K31/44 // (C07D471/04, 207:00,
213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 98 45295 A (NEUROGEN CORPORATION) 15 October 1998 see claims 1-21 ---	1-56
Y	WO 94 13676 A (PFIZER INC.) 23 June 1994 see claims 1-13 ---	1-55
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P, Y	WO 98 29397 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 9 July 1998 see claims 1-14 ---	1-56
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or
5 facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound of formula in Claim 1.

10 56. A process for the preparation of a compound as claimed in Claim 1.

52. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

5 53. A method for the treatment or prevention of physiological disorders associated with an excess of CRF, which method comprises administration to a patient in need thereof a CRF-reducing amount of a compound according to Claim 1.

10 54. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or
15 alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or
20 a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound of formula in any one of Claims
25 1.

30 55. The use of a compound for the manufacture of a medicament for the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems,

44. A compound according to Claim 1 which is 4-(N-(2-Diethylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

5

45. A compound according to Claim 1 which is 4-(N-(2-Diethylaminoethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

10

46. A compound according to Claim 1 which is 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

15

47. A compound according to Claim 1 which is 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,6-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

20

48. A compound according to Claim 1 which is 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole).

25

49. A compound according to Claim 1 which is 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

50. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-butyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

30

51. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-propyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

36. A compound according to Claim 1 which is 4-(N-(2-Pyrrolidinoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,6-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

5 37. A compound according to Claim 1 which is 4-(N-(2-(4-Triazolyl)ethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

10 38. A compound according to Claim 1 which is 4-(N-(2-(2-Methoxyethyl)aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

15 39. A compound according to Claim 1 which is 4-(N-(2-(2-Methylimidazolinyl)ethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

20 40. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

25 41. A compound according to Claim 1 which is 4-(N-(2-(Phenylmethyl)aminoethyl)-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

30 42. A compound according to Claim 1 which is 4-(N-2-(4-Methylpiperazinyl)ethyl-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

43. A compound according to Claim 1 which is 4-(N-(2-Pyrrolidinoethyl)-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

29. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

5

30. A compound according to Claim 1 which is 4-(N-(2-Pyrrolidinoethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

10

31. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

15

32. A compound according to Claim 1 which is 4-(N-(2-Ethylmethylamino)ethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

20

33. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-2-methoxyethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

25

34. A compound according to Claim 1 which is 4-(N-(2-Dimethylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole.

30

35. A compound according to Claim 1 which is 4-(N-(2-Pyrrolidinoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

20. A compound according to claim 18, wherein A^2 is (C_3-C_5)cycloalkyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1-C_3 alkyl.

5

21. A compound according to claim 18, wherein at least one R_a is methyl; A^2 is (C_3-C_5)cycloalkyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1-C_3 alkyl.

10

22. A compound according to claim 18, wherein each R_a is methyl; A^2 is cyclopropyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1-C_3 alkyl.

15

23. A compound according to claim 18, wherein m is 1.

24. A compound according to claim 16, wherein m is 2.

25. A compound according to claim 21, m is 1 and R^1 is C_1-C_3 alkyl.

20

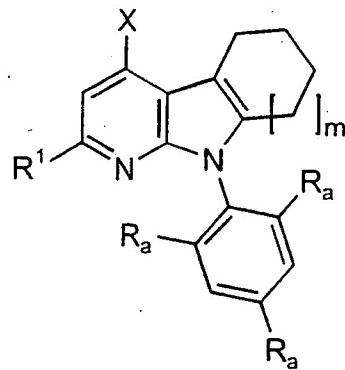
26. A compound according to Claim 1 which is 4-(N -(2-Pyrrolidinoethyl)- N -cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

25

27. A compound according to Claim 1 which is 4-(N -(2-Morpholinoethyl)- N -cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.

30

28. A compound according to Claim 1 which is 4-(N -2-(4-Methylpiperazinyl)ethyl- N -cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole.



wherein X, m, and R¹ are as defined in claim 1; and each R_a is halogen, trifluoromethyl, hydroxy, amino, C₁-C₆ alkyl, or C₁-C₆ alkoxy.

5

17. A compounds according to claim 16, wherein V¹ and V² represent methylene; Y¹ is a bond; A¹ represents pyrrolidinyl, morpholinyl, piperazinyl, or mono- or di-C₁-C₆ alkyl; Y² represents a bond or methylene; and A² represents C₁-C₆ alkyl or C₁-C₆ alkoxyethyl.

10

18. A compound according to claim 16, wherein each R_a independently represents C₁-C₆ alkyl;

15 A² is (C₃-C₅)cycloalkyl(C₁-C₄)alkyl or (C₃-C₅)cycloalkyl; A¹ is

NR⁴R⁵ where R⁴ and R⁵ are independently hydrogen, C₁-C₆ alkyl; or

20 NR⁴R⁵ forms a 5 or 6-membered nitrogen heterocycle optionally containing an oxygen or second nitrogen atom;

Y¹ is C₁-C₆ alkylene;

Y² is a bond or C₁-C₆ alkylene;

V¹ is methylene; and V² is methylene.

25 19. A compound according to claim 16, wherein A² is cyclopropyl(C₁-C₃)alkyl or (C₃-C₅)cycloalkyl; and R⁴ and R⁵ are independently C₁-C₆ alkyl.

at least one R_a is C_1-C_6 alkyl and the other R_a groups are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy or trifluoromethyl;

A^2 is (C_3-C_5) cycloalkyl (C_1-C_4) alkyl or (C_3-C_5) cycloalkyl;

5 A^1 is

NR^4R^5 where R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl; or

10 NR^4R^5 forms a 5 or 6-membered nitrogen heterocycle optionally containing an oxygen or second nitrogen atom;

Y^1 is C_1-C_6 alkylene;

Y^2 is a bond or C_1-C_6 alkylene;

V^1 is methylene; and V^2 is methylene.

15 13. A compound according to claim 10, wherein A^2 is cyclopropyl (C_1-C_3) alkyl or (C_3-C_5) cycloalkyl; and R^4 and R^5 are independently C_1-C_6 alkyl.

20 14. A compound according to claim 12, wherein A^2 is (C_3-C_5) cycloalkyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1-C_3 alkyl.

25 15. A compound according to claim 12, where each R_a is methyl; A^2 is cyclopropyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1-C_3 alkyl.

16. A compound according to claim 1, which is

6. A compound according to claim 5, wherein A^2 is (C_3-C_5)cycloalkyl.

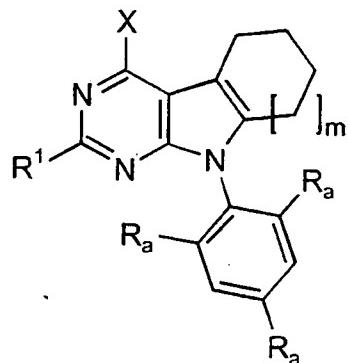
7. A compound according to claim 6, wherein R^4 and R^5 5 are independently C_1-C_6 alkyl.

8. A compound according to claim 5, wherein at least one R_a is methyl; Y^2 is a bond; and R^4 and R^5 are the same and represent C_1-C_3 alkyl.

10

9. A compound according to claim 1, wherein m is 1 and R^1 is C_1-C_3 alkyl.

10. A compound according to claim 1, which is



15

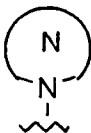
wherein X, m, and R^1 are as defined in claim 1; and each R_a is halogen, trifluoromethyl, hydroxy, amino, C_1-C_6 alkyl, or C_1-C_6 alkoxy.

20

11. A compound according to claim 10, wherein V^1 and V^2 represent methylene; Y^1 is a bond; A^1 represents pyrrolidinyl, morpholinyl, piperazinyl, or mono- or di- C_1-C_6 alkyl; Y^2 represents a bond or methylene; and A^2 represents C_1-C_6 alkyl or C_1-C_6 alkoxyethyl.

25

12. A compound according to claim 10, where



wherein the N-ring represents triazolyl, tetrazolyl, imidazolyl, pyrazolyl, each of which is optionally substituted with amino, trifluoromethyl, carboxamido, or (C_1-C_6 alkylene) 6 - R^{12} wherein G^6 is NH, $NH(C_1-C_6$ alkyl) and R^{12} is hydrogen or C_1-C_6 alkyl.

2. A compound according to claim 1, wherein V^1 and V^2 represent methylene; Y^1 is a bond; A^1 represents pyrrolidinyl, morpholinyl, piperazinyl, or mono- or di- C_1-C_6 alkyl; Y^2 represents a bond or methylene; and A^2 represents C_1-C_6 alkyl or C_1-C_6 alkoxyethyl.

15 3. A compound according to claim 1, wherein each R_a independently represents C_1-C_6 alkyl; and A^2 is C_1-C_6 cycloalkyl.

4. A compound according to claim 1, where A^2 is (C_3-C_5)cycloalkyl(C_1-C_4)alkyl.

20

5. A compound according to claim 1, where
 A^1 is

NR^4R^5 where R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl; or

25 NR^4R^5 forms a 5 or 6-membered nitrogen heterocycle optionally containing an oxygen or second nitrogen atom;

Y^1 is C_1-C_6 alkylene;

Y^2 is a bond or C_1-C_6 alkylene;

30 V^1 is methylene; and V^2 is methylene.

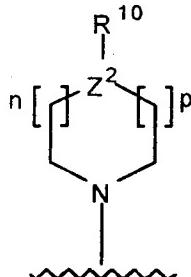
5

wherein heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-pyrazinyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally mono- or disubstituted with halogen, trifluoromethyl, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, with the proviso that tetraazolinyl can have at most one substituent;

10 Z¹ is C₁-C₆ alkyl; and

V², Y² and A² are as defined above;

(iii)



wherein

Z² is carbon or nitrogen;

wherein

15 when Z² is CH, n is 0, 1, 2 or 3 and p is 1, 2, or 3,

R¹⁰ is carboxamido, or (C₁-C₆ alkylene)-G⁵-R¹¹

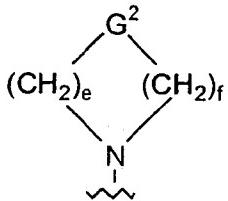
wherein G⁵ is NH, NH(C₁-C₆ alkyl) and R¹¹ is hydrogen or C₁-C₆ alkyl;

20 when Z² is carbon, n is 1 or 2 and p is 1 or 2, R¹⁰ is amino; or

when Z² is nitrogen, n is 1 or 2 and p is 1 or 2, R¹⁰ is hydrogen; or

(iv) a nitrogen heterocycle of the formula:

A¹ is NR⁴R⁵ wherein R⁴ and R⁵ are independently hydrogen or a C₁-C₆ alkyl group which and optionally forms a heterocycloalkyl group with Y¹; acetyl or sulfonyl with the proviso that R⁴ and R⁵ cannot both be acetyl or sulfonyl; or NR⁴R⁵ taken together form a C₃-C₆ heterocycloalkyl or a group of the formula:



wherein e and f are independently 1, 2, or 3 and the sum of e and f is at least 3; and

G² is

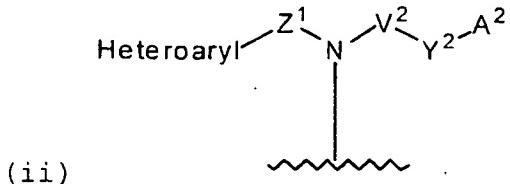
NR⁶ wherein R⁶ is hydrogen or C₁-C₆ alkyl, or

CH(C₀-C₆ alkylene)-G³-R⁷ wherein G³ is CONH,

CONH(C₁-C₆ alkyl), NH, NH(C₁-C₆ alkyl) and R⁷ is hydrogen or C₁-C₆ alkyl; or

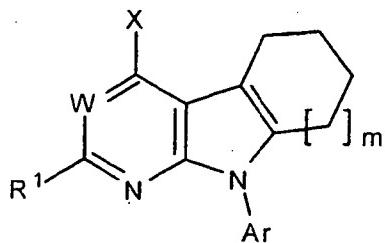
CONH₂, CO[N(C₁-C₆ alkyl)R⁸] wherein R⁸ is hydrogen or C₁-C₆ alkyl;

A² is hydrogen, C₁-C₆ alkyl, (C₁-C₆ alkylene)-G⁴-R⁹ wherein G⁴ is oxygen or sulfur and R⁹ is hydrogen, trifluoromethyl or C₁-C₆ alkyl;



WHAT IS CLAIMED IS:

1. A compound of the formula:

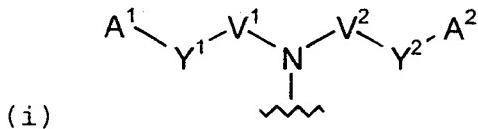


or the pharmaceutically acceptable salts thereof wherein:

- 5 Ar is phenyl, 1- or 2-naphthyl, 2-, 3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, optionally mono-, di-, or tri-substituted with halogen, trifluoromethyl, hydroxy, amino, carboxamido, C₁-C₆ alkyl, C₁-C₆ alkoxy, with the proviso that at least one of the positions ortho or para to the point of attachment of Ar to the tricyclic ring system is substituted;

- 10 R¹ is hydrogen, halogen, trifluoromethyl, C₁-C₆ alkyl, or (C₁-C₆ alkyl)-G¹-R² where G¹ is oxygen or sulfur and R² is hydrogen or C₁-C₆ alkyl;
- 15 W is N or C-R³ where R³ is hydrogen or C₁-C₆ alkyl;
- m is 0, 1, or 2;

X is



wherein

- 20 V¹ and V² are CH₂, CO, CS, SO₂ or CH(C₁-C₆ alkyl), with the proviso that both V¹ and V² cannot both be CO, CS or SO₂;

- V¹ and V² independently represent a bond or C₁-C₆ alkylene;

minutes at 4°C. Pellets are re-suspended, homogenized and centrifuged two additional times. The receptor binding assay is performed using assay buffer (50 mM Tris HCl, 10 mM MgCl₂, 2 mM EGTA, pH 7.4, 0.1% BSA, 0.1 mM bacitracin (22.0mg/100 mL)), 5 150 µg protein/tube, and [¹²⁵I]Sauvagine (NEN; 100 pM for competition analysis and 10 pM-1 nM for saturation analysis) to yield a final volume of 200 uL. Nonspecific binding is defined using 2 uM r/h CRF or 9-41 alpha-helical CRF. Cells are incubated for 2 hours at room temperature. The assay is 10 terminated by rapid vacuum filtration (Tomtec: Deepwell 3) through GFC filters presoaked in 1% PEI using ice-cold 50 mM Tris HCl and dry thoroughly by air. Specific Binding: 70-80%; Kd (nM): 0.30 nM; Bmax (fmole/mg protein): 40-50. IC₅₀ values are calculated with the non-linear curve fitting program RS/1 15 (BBN Software Products Corp., Cambridge, MA).

The binding affinity for the compounds of Formula I expressed as IC₅₀ value, generally ranges from about 0.5 nanomolar to about 10 micromolar.

20 The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the 25 present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

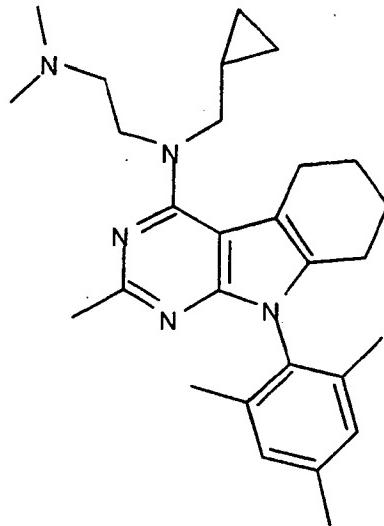
containing 10 mM MgCl₂ and 2 mM EDTA and centrifuged for 10 minutes at 48000g. Membranes are washed again and brought to a final concentration of 1500mg/ml in binding buffer (Tris buffer above with 0.1 % BSA, 15 mM bacitracin and 0.01 mg/ml aprotinin.). For the binding assay, 100 ml of the membrane preparation is added to 96 well microtube plates containing 100 ml of ¹²⁵I-CRF (SA 2200 Ci/mmol, final concentration of 100 pM) and 50 ml of drug. Binding is carried out at room temperature for 2 hours. Plates are then harvested on a Brandel 96 well cell harvester and filters are counted for gamma emissions on a Wallac 1205 Betaplate liquid scintillation counter. Non specific binding is defined by 1 mM cold CRF. IC₅₀ values are calculated with the non-linear curve fitting program RS/1 (BBN Software Products Corp., Cambridge, MA). The binding affinity for the compounds of Formula I expressed as IC₅₀ value, generally ranges from about 0.5 nanomolar to about 10 micromolar.

Alternatively, the binding activity of the compounds of formula I to the human CRF₁ receptor can be measured as follows:

Assay for Human CRF Receptor Binding Activity in IMR32 cells

[¹²⁵I]Sauvagine Binding to CRF₁ Receptors Endogenously Expressed in IMR-32 Cells: IMR-32 human neuroblastoma cells are grown to 80% confluence in EMEM containing Earle's Balanced Salts and 2 mM l-glutamine with 10% FBS, 25 mM HEPES, 1 mM Sodium Pyruvate, and nonessential amino acids. At this time, flasks of cells are treated with 2.5 uM 5-bromo-2'-deoxyuridine (Br-dU) for 10 days. Media is changed every 3-4 days across the 10 day period. Cells are harvested using No-Zyme (JRH Biosciences) and rinsed with PBS. For membrane preparation, cells are homogenized in wash buffer (50 mM Tris HCl, 10 mM MgCl₂, 2 mM EGTA, pH 7.4) and centrifuged at 48,000 x g for 10

D. 4-(N-(2-Dimethylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole (Compound 41)



5 To a solution of the compound from Example 6C (650 mg) in N,N-dimethylformamide (5 mL) at 0 C, under a blanket of nitrogen, is added sodium hydride (60%, 280 mg). After stirring the solution for 0.5 hours, 2-dimethylaminoethyl chloride hydrochloride (500 mg) is added. The mixture is then
 10 heated to 40 C for 2 hours, then quenched with ice and water. Dilute with ethyl acetate and wash with water, brine, dry over sodium sulfate, filter and concentrate. Purify by radial chromatography using 10% methanol and 0.5% ammonium hydroxide in dichloromethane as eluant to obtain 450 mg of product: MS
 15 446 (M+H).

Example 7

The pharmaceutical utility of compounds of this invention is indicated by the assays shown in the following examples for human CRF1 receptor activity.

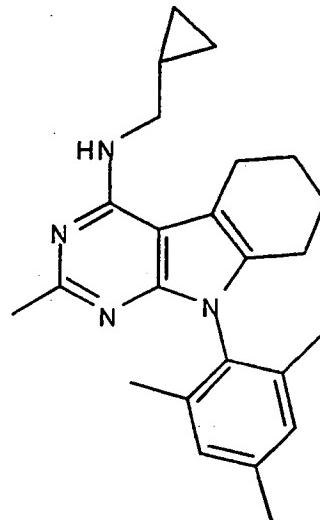
20 Assay for CRF Receptor Binding Activity

CRF receptor binding is performed using a modified version of the assay described by Grigoriadis and De Souza (*Methods in Neurosciences*, Vol. 5, 1991). Membrane pellets containing CRF receptors are resuspended in 50mM Tris buffer pH 7.7

dichloromethane. The combined extracts are dried over sodium sulfate, filtered and concentrated to give a tan colored solid: MS 340 (M+H).

5

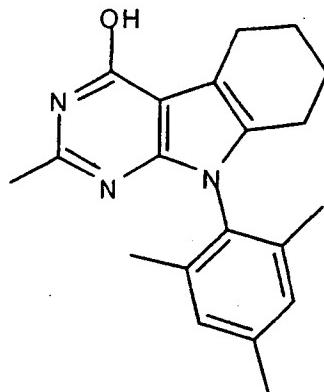
C. 4-Cyclopropylmethylamino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole



A mixture containing the compound from Example 6B (1.0 g) and cyclopropylmethylamine (1.6 g) in N-methylpyrrolidinone (4 mL) is heated to 100 C in a sealed tube for 24 hours. Dilute mixture with ethyl acetate and wash with water, aqueous ammonium chloride, aqueous sodium bicarbonate, and brine. Dry over sodium sulfate, filter and concentrate to give a tan colored solid. Purify by radial chromatography using 30% ethyl acetate in hexanes as eluant to give 660 mg of product: MS 375 (M+H).

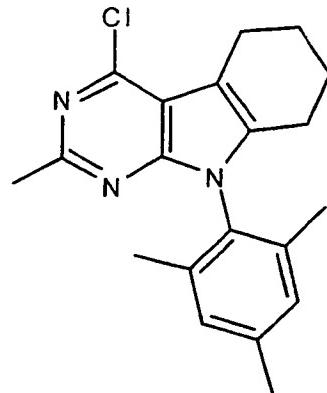
Example 6

A. 4-Hydroxy-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole



5 A mixture of the compound from Example 1A (5.0 g), acetic anhydride (1.9 mL) and acetic acid (5 mL) is refluxed for 1 hour then, concentrated to a solid. Phosphoric acid (5 mL, 85%) is added to the amide. The mixture is then refluxed for 0.5 hours and cooled to ambient temperature. The solution is
10 poured onto ice and the precipitate that forms is collected by filtration: MS 322 (M+H).

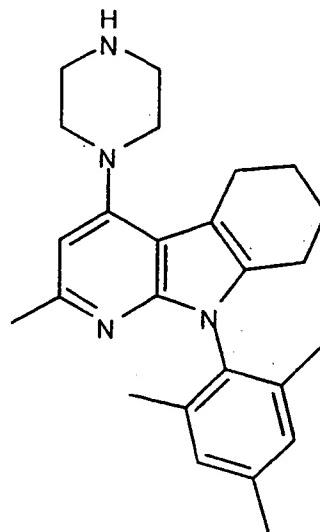
B. 4-Chloro-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyrimidino[4,5-b]indole



15

The compound from Example 6A (4.4 g) is refluxed in phosphoryl chloride (35 mL) for 3 hours. The excess phosphoryl chloride is removed under reduced pressure and the residue is partitioned between aqueous sodium bicarbonate and dichloromethane. The aqueous is extracted with more
20 dichloromethane.

B. 4-Piperazinyl-2-methyl-9-(2,4,6-trimethylphenyl)-
5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole



5 Combine the compound from Example 5A (200 mg) and piperazine (0.58 g) in N-methylpyrrolidinone (2 mL) and heat the solution to 120 °C for 12 hours. Pour mixture into water and extract with ethyl acetate. Wash extract with aqueous ammonium chloride then water. Dry extract over sodium sulfate,
10 filter and concentrate. Purify by preparative tlc using 10% methanol in dichloromethane as eluant.

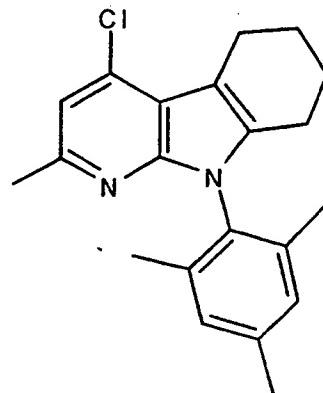
a) 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,6-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 403 (M+H). (Compound 38)

5 b) 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 417 (M+H). (Compound 39)

10 c) 4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 403 (M+H). (Compound 40)

Example 5

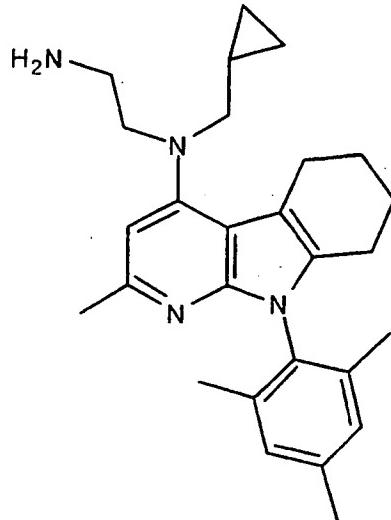
A. 4-Chloro-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole



Dissolve tert-butylnitrite (0.65 g) in acetonitrile (10 mL) and add copper(II)chloride (0.68 g). Then the compound from Example 1B (1.33 g) is added portionwise to the greenish-brown solution and the mixture is stirred for 12 hours. The acetonitrile is removed by evaporation and the residue is partitioned between water and dichloromethane. The aqueous layer is extracted with more dichloromethane and the combined extract is washed with water, dried over sodium sulfate, filtered and concentrated. The product is filtered through a plug of silica gel using 20% ethyl acetate in hexanes as eluant to afford a tan colored solid.

Example 3

4-(N-(2-Aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-blindole (Compound 37)



5

A solution containing the product from Example 1D (500 mg) and sodium azide (22 mg) in N-methylpyrrolidinone (5 mL) is heated to 120°C for 2 hours. The mixture is poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated. An ethanol (10 mL) solution of the crude product and 10% palladium on carbon (about 200 mg) is hydrogenated for 8 hours at approximately 1 atmosphere pressure. The suspension is filtered over celite and concentrated. The product is purified by preparative tlc using 20% ethyl acetate in hexanes as eluant, followed by 10% methanol in dichloromethane and converted to the hydrochloride salt: MS (freebase) 417 (M+H).
10
15

20

Example 4

The following compounds are prepared essentially according to the procedures set forth above in Example 3.

gg) 4-(N-(2-Pyrrolidinoethyl)-N-propyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 459 (M+H). (Compound 34)

5 hh) 4-(N-(2-Pyrrolidinoethyl)-N-butyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 473 (M+H). (Compound 35)

10 ii) 4-(N-(2-Pyrrolidinoethyl)-N-(2-methoxyethyl))amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 475 (M+H). (Compound 36)

- z) 4 - (N- (2-Dimethylaminoethyl) -N-
cyclopropylmethyl) amino-2-methyl-9- (2,6-dimethylphenyl) -
5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 431 (M+H).
5 (Compound 27)
- aa) 4 - (N- (2-Pyrrolidinoethyl) -N- (1-oxoethyl)) amino-2-
methyl-9- (2,4,6-trimethylphenyl) -5,6,7,8-tetrahydro-9H-
pyridino[2,3-b]indole: MS 459 (M+H). (Compound 28)
10
- bb) 4 - (N- (2-Pyrrolidinoethyl) -N- (1-oxopropyl)) amino-2-
methyl-9- (2,4,6-trimethylphenyl) -5,6,7,8-tetrahydro-9H-
pyridino[2,3-b]indole: MS 473 (M+H). (Compound 29)
- cc) 4 - (N- (2-Dimethylaminoethyl) -N-
cyclopropylmethyl) amino-2-methyl-9- (2,4-dimethylphenyl) -
5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 431 (M+H).
15 (Compound 30)
- dd) 4 - (N- (2-Pyrrolidinoethyl) -N- (1-oxobutyl)) amino-2-
methyl-9- (2,4,6-trimethylphenyl) -5,6,7,8-tetrahydro-9H-
pyridino[2,3-b]indole: MS 487 (M+H). (Compound 31)
20
- ee) 4 - (N- (2-Pyrrolidinoethyl) -N- (2-methoxy-1-
25 oxoethyl)) amino-2-methyl-9- (2,4,6-trimethylphenyl) -5,6,7,8-
tetrahydro-9H-pyridino[2,3-b]indole: MS 489 (M+H). (Compound
32)
- ff) 4 - (N- (2-Pyrrolidinoethyl) -N-ethyl) amino-2-methyl-9-
30 (2,4,6-trimethylphenyl) -5,6,7,8-tetrahydro-9H-pyridino[2,3-
b]indole: MS 445 (M+H). (Compound 33)

r) 4-(N-(2-Diethylaminoethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 475 (M+H). (Compound 19)

5 s) 4-(N-(2-Dimethylaminoethyl)-N-ethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 419 (M+H). (Compound 20)

10 t) 4-(N-(2-Dimethylaminoethyl)-N-butyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 447 (M+H). (Compound 21)

15 u) 4-(N-(2-Dimethylaminoethyl)-N-propyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 433 (M+H). (Compound 22)

v) 4-(N-(2-Methylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 431 (M+H). (Compound 23)

20 w) 4-(N-(2-(Ethylmethylamino)ethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 459 (M+H). (Compound 24)

25 x) 4-(N-(2-Dimethylaminoethyl)-N-cyclopropyloxomethyl)amino-2-methyl-10-(2,4,6-trimethylphenyl)-5,6,7,8,9-pentahydrocyclohepta[1,2-d]pyridino[2,3-b]pyrrole: MS 473 (M+H). (Compound 25)

30 y) 4-(N-(2-Dimethylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-10-(2,4,6-trimethylphenyl)-5,6,7,8,9-pentahydrocyclohepta[1,2-d]pyridino[2,3-b]pyrrole: MS 459 (M+H). (Compound 26)

j) 4-(N-(2-Dimethylaminoethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 447 (M+H). (Compound 11)

5 k) 4-(N-(2-(Ethylmethylamino)ethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 461 (M+H). (Compound 12)

10 l) 4-(N-(2-Dimethylaminoethyl)-N-2-methoxyethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 449 (M+H). (Compound 13)

15 m) 4-(N-(2-Dimethylaminoethyl)-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 433 (M+H). (Compound 14)

20 n) 4-(N-(2-(Phenylmethyl)aminoethyl)-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 495 (M+H). (Compound 15)

o) 4-(N-2-(4-Methylpiperazinyl)ethyl-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 488 (M+H). (Compound 16)

25 p) 4-(N-(2-Pyrrolidinoethyl)-N-isopropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 459 (M+H). (Compound 17)

30 q) 4-(N-(2-Diethylaminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 473 (M+H). (Compound 18)

c) 4-(N-(2-Pyrrolidinoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,6-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 457 (M+H). (Compound 4)

5 d) 4-(N-(2-Morpholinoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 487 (M+H). (Compound 5)

10 e) 4-(N-2-(4-Methylpiperazinyl)ethyl-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 500 (M+H). (Compound 6)

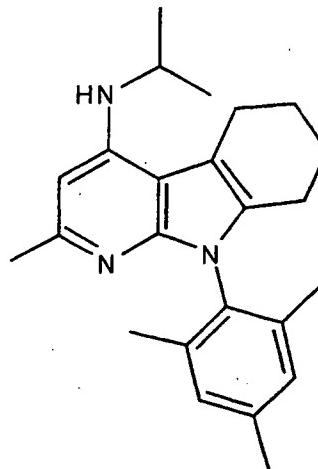
15 f) 4-(N-(2-(4-Triazolyl)ethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 469 (M+H). (Compound 7)

20 g) 4-(N-(2-(2-Methoxyethyl)aminoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 475 (M+H). (Compound 8)

25 h) 4-(N-(2-(2-Methylimidazolinyl)ethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 484 (M+H). (Compound 9)

30 i) 4-(N-(2-Pyrrolidinoethyl)-N-2-methylpropyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 473 (M+H). (Compound 10)

F. 4-Cyclopropylamino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole



To a solution containing the product from Example 1B (2 g) and 2-methoxypropene (10 mL) in dichloroethane (25 mL) are added acetic acid (0.4 mL) and sodium triacetoxyborohydride (5 g). The mixture is stirred at room temperature for 24 hours then concentrated. Dissolve residue in ethyl acetate and wash with water, followed by 1N sodium hydroxide and brine. Dry extract over sodium sulfate, filter and concentrate: MS 362 (M+H).

Example 2

The following compounds are prepared essentially according to the procedures set forth above for Example 1.

a) 4-(N-(2-Pyrrolidinoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 471 (M+H). (Compound 2)

20

b) 4-(N-(2-Pyrrolidinoethyl)-N-cyclopropylmethyl)amino-2-methyl-9-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole: MS 457 (M+H). (Compound 3)

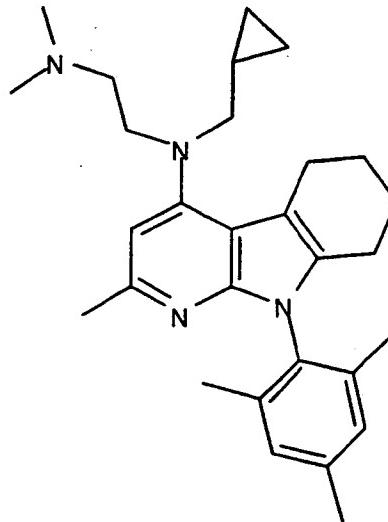
Alternatively, the above compound can be prepared from 4-(N-Cyclopropyloxomethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole described in Example IC. To a suspension of the latter amide (20g, 0.052 mol) and N,N-dimethylaminoethyl chloride hydrochloride (10g, 0.069 mol) in N,N-dimethylformamide (200 mL) is added sodium hydride (60% in mineral oil, 6.0g, 0.15 mol) slowly in portions over a 30-min period with stirring. After the addition is complete, the mixture is warmed to 60 C for 2.5 h, cooled to 0 C, diluted by water (100 mL), and acidified by adding 2N HCl (150 mL). The aqueous solution is washed with hexane to remove mineral oil, treated with activated carbon (2g), heated to 80 C for 30 min, filtered while hot, and allowed to cool to room temperature. The filtrate is slowly poured into a vigorously stirred, ice-cold solution of NaOH (40mL of 10N NaOH in ice-water to make 500mL). After 30 min of stirring, the slurry is filtered, air-dried and recrystallized from hexane to give 15 g of a white solid.

The latter aminoamide (20.5 g, 44.70 mmol) is dissolved in 100 mL anhydrous THF and added dropwise to an ice-cold, stirring solution of DIBAL-H (100 mL, 1.5M in toluene, 3 equiv.) in 200 mL anhydrous toluene under an atmosphere of N₂. The mixture is allowed to warm to rt over 6 hours. The mixture is cooled again and carefully quenched with a saturated solution of Na₂SO₄, diluted with some toluene, and filtered to remove the inorganic solids. The filtrate is washed with water, brine then dried over Na₂SO₄ and filtered. The solvent is removed in vacuo to afford 19.5 g of oil that solidifies upon standing.

for 15 minutes then for 1 hour at reflux temperature. The solution is cooled back to room temperature, quenched with a large excess of methanol (50 mL) and reheated to reflux for 1 hour. The solution is then concentrated: MS 436 (M+H).

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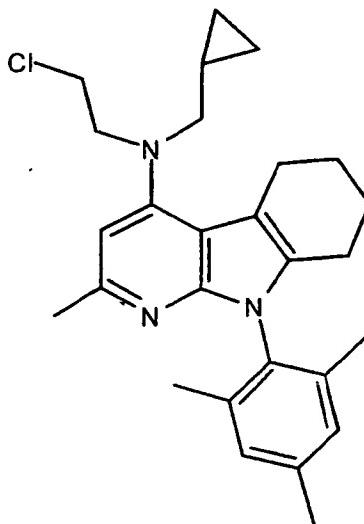
E. 4-(N-(2-Dimethylaminoethyl)-N-
cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-
5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole (Compound 1)



10 A steel bomb containing the product from Example 1D (3.8 g), dimethylamine (8 mL) and N-methylpyrrolidinone (20 mL) is sealed and heated to 80°C for 10 hours. The mixture is poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried over sodium sulfate, 15 filtered and concentrated. The product is purified by crystallization of the sulfate salt: Concentrated sulfuric acid (0.46 mL) is added to the isolated amino compound (3.9 g) dissolved in ethanol (5 mL). The solution is concentrated to dryness and subsequently dissolved in isopropanol (5 mL).
 20 Next ethyl acetate (20 mL) is added and the solution is allowed to stand at room temperature. The white crystals that form are collected by filtration: MS (free base) 445 (M+H).

concentrated to give 4-(N-Cyclopropylloxomethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole. The latter compound is dissolved in THF (100 mL) and mixed with borane-methyl sulfide complex (10M, 10.3 mL). The
 5 mixture is heated to reflux for 8 hours and quenched at room temperature with a large excess of methanol (about 100 mL). Reheat mixture to reflux for 1 hour, then concentrate under reduced pressure. More methanol (another 50 mL) is added to the gummy residue and the solution is re-concentrated to yield a
 10 white solid: MS 374 (M+H).

D. 4-(N-(2-Chloroethyl)-N-cyclopropylmethyl)amino-2-
methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-
pyridino[2,3-b]indole



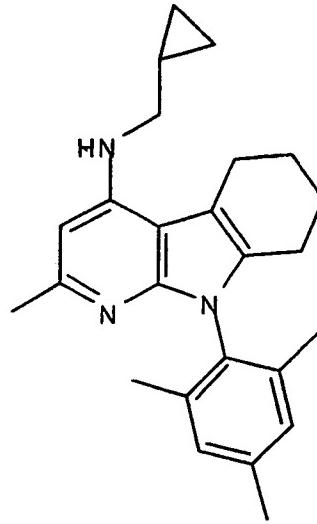
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A solution containing the product from Example 1C (13 g) and chloroacetyl chloride (3 mL) in dichloroethane (100 mL) is refluxed for 4 hours. The solvent and excess reagent are removed under reduced pressure. Aqueous potassium carbonate is added to the remaining oily residue and extracted with dichloromethane. The extract is dried with sodium sulfate, filtered and concentrated. The latter chloroacetyl compound (15 g) is dissolved in THF (100 mL). Add borane-methyl sulfide complex (10M, 3.4 mL) and stir at ambient temperature
 20

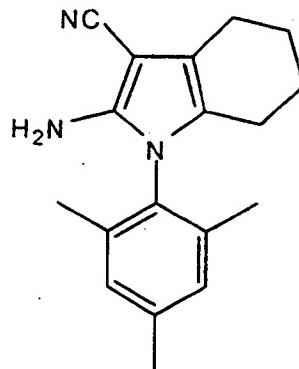
toluenesulfonic acid monohydrate (3.6 g). The mixture is refluxed for 1 hour then the solvent is removed by distillation. The residue is dissolved in THF (3 L) and cooled to 0°C. To this solution, under an atmosphere of nitrogen gas, 5 is added LDA (2.0M, 1.2 L) at a rate to keep the reaction internal temperature below 10°C. After 3 hours the reaction is neutralized with aqueous HCl. The aqueous layer is extracted with ethyl acetate and combined with the THF layer. The combined organic phase is extracted with 3M HCl and the latter 10 is made alkaline (pH=10) with 10N NaOH and ice. The aqueous solution is extracted with dichloromethane, dried with sodium sulfate, filtered and concentrated to give a crystalline solid: MS 320 (M+H).

15

C. 4-(N-Cyclopropylmethyl)amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole



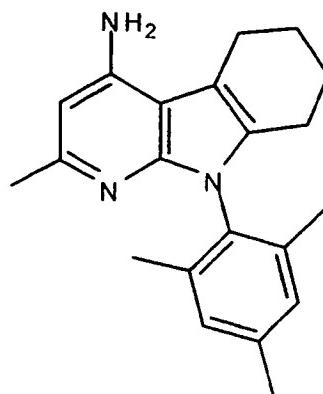
A solution of dichloroethane (70 mL) containing the product of Example 1B (11 g) and cyclopropanecarbonyl chloride 20 (3.4 mL) at reflux is treated with dropwise addition of N,N-diisopropylethylamine (6.6 mL). After heating for 0.5 hour the reaction is cooled to ambient temperature and poured into aqueous potassium carbonate solution. The product is extracted with dichloromethane, dried over sodium sulfate, filtered and

Example 1A. 2-Amino-4,5,6,7-tetrahydro-1-phenyl-1H-indole-3-carbonitrile

5 A mixture of 2,4,6-trimethylaniline (500 g) and adipoin (464 g) in toluene (2.5 L) is heated to reflux. A theoretical amount of water is removed azeotropically over the course of 3 hours. The mixture is cooled to ambient temperature, then malononitrile (244 g) and ammonium acetate (57 g) are added.

10 The reaction is slowly reheated back to reflux for about 1 hour with azeotropic removal of water. After cooling, the precipitate that forms overnight is collected by filtration. The dark solid is washed with ethanol and dried to afford 540 g of a white powder: MS 280 (M+H).

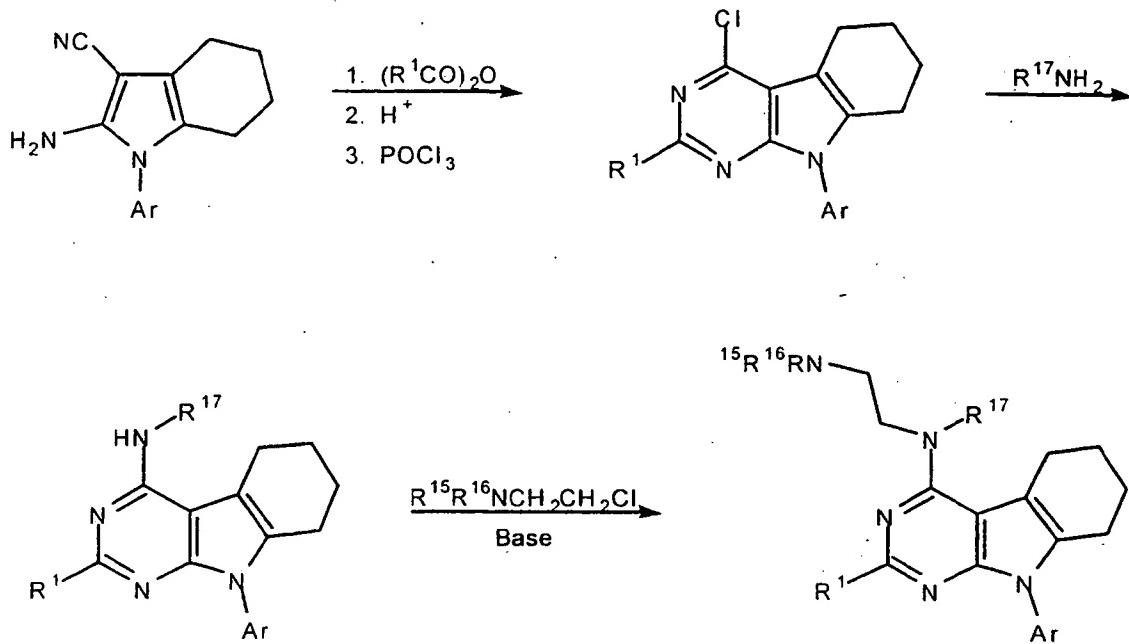
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B. 4-Amino-2-methyl-9-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydro-9H-pyridino[2,3-b]indole

To the product of Example 1A (535 g) dissolved in

20 dichloroethane (4 L) are added 2-methoxypropene (550 mL) and p-

Scheme IV



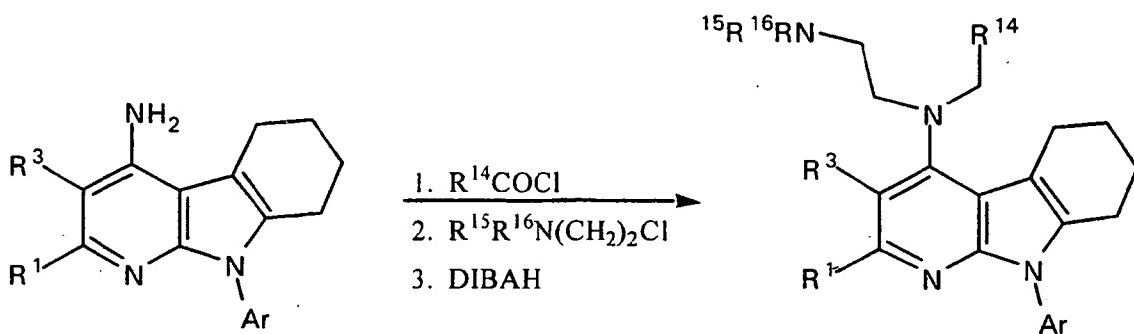
wherein Ar and R¹ are as defined with reference to
 5 Formula I; R¹⁵, R¹⁶ and R¹⁷ are as defined above in Formula I
 with respect to the definition of X;

The preparation of the compounds of the present invention
 is illustrated further by the following examples, which are not
 10 to be construed as limiting the invention in scope or spirit to
 the specific procedures and compounds described in them.

The disclosures of all articles and references mentioned
 in this application, including patents, are incorporated
 herein by reference.

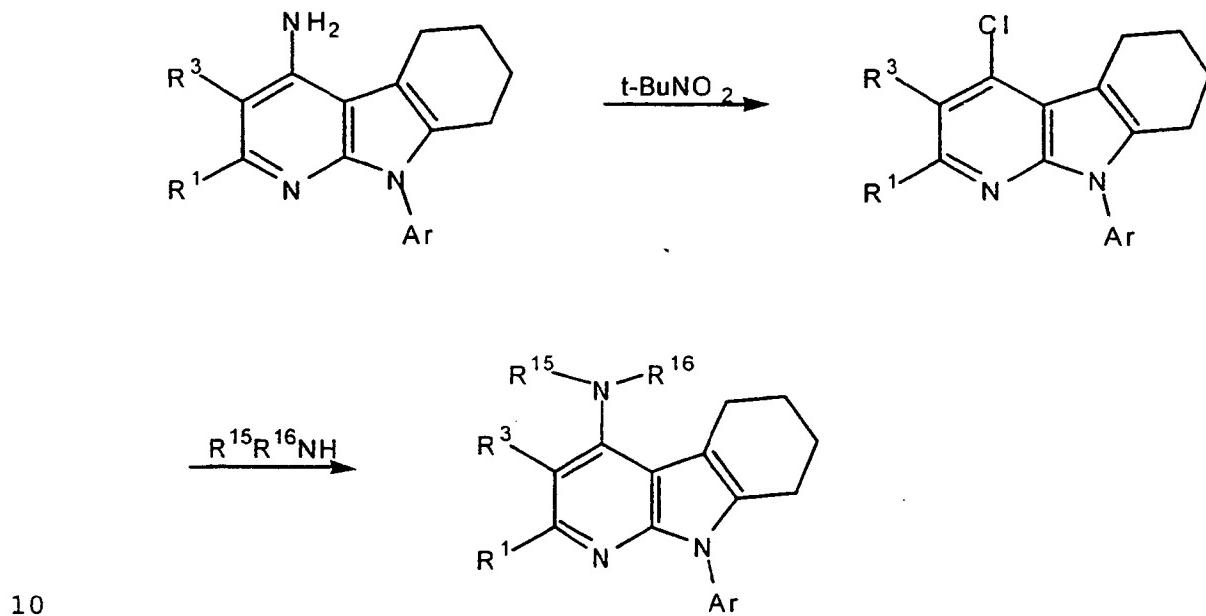
15 Commercial reagents were used without further
 purification. THF refers to tetrahydrofuran. LDA refers to
 lithium diisopropylamide. Room or ambient temperature refers
 to 20 to 25 C. Concentration implies the use of a rotary
 evaporator. TLC refers to thin layer chromatography. Mass
 20 spectral data were obtained either by CI or APCI methods.

Scheme II



5 wherein Ar, R¹ and R³ are as defined above for Formula I;
and R¹⁴, R¹⁵ and R¹⁶ are encompassed by the definition of X in
Formula I;

Scheme III



10

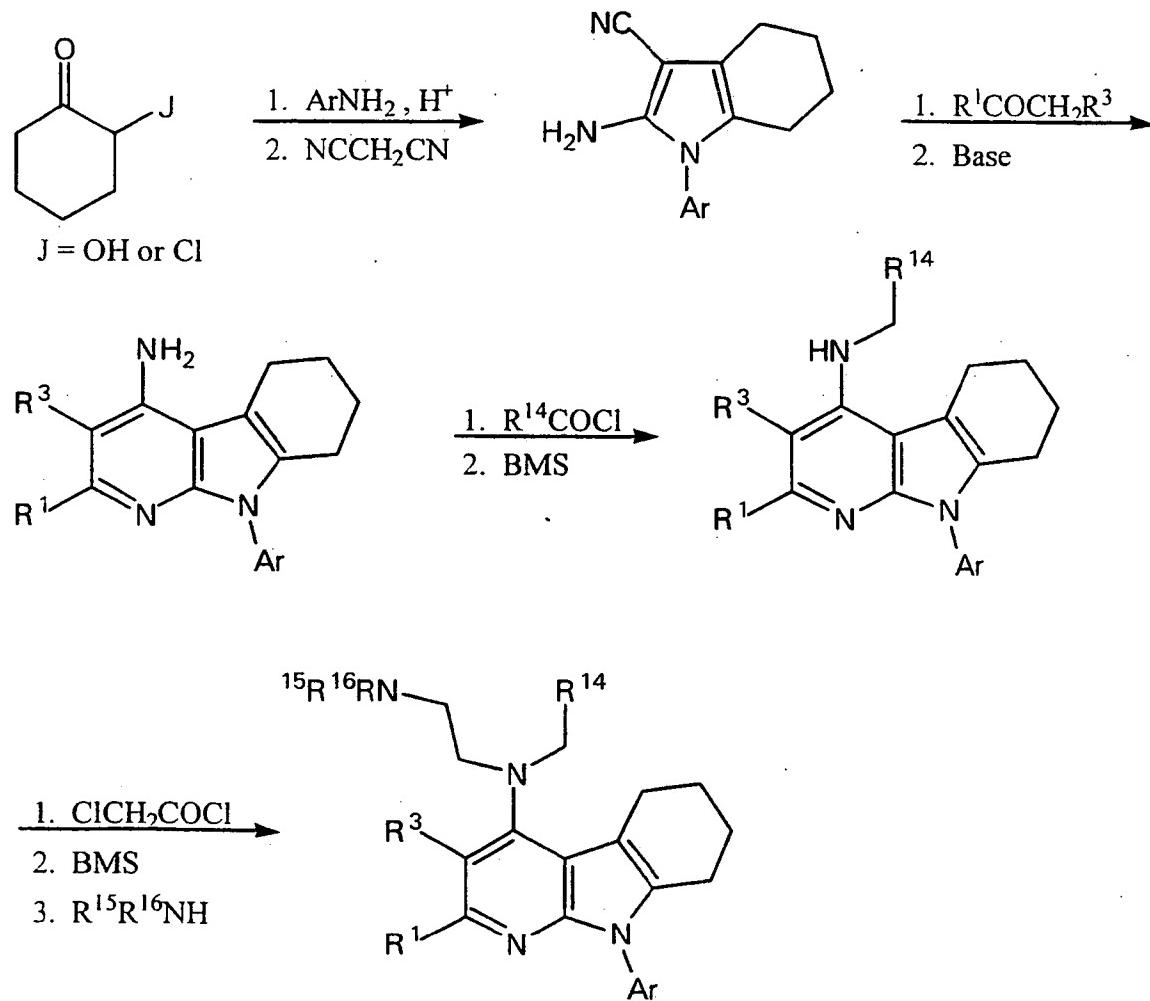
wherein Ar, R¹ and R³ are as defined above for Formula I;
and R¹⁵ and R¹⁶ are encompassed by the definition of X in
Formula I;

Preparation of Aminoalkyl Substituted 5,6,7,8-Tetrahydro-9H-Pyridino[2,3-b]indole and 5,6,7,8-Tetrahydro-9H-Pyrimidino[4,5-b]indole Analogues

5 Representative preparations of compounds of the present invention are shown in Schemes I, II, III and IV. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.

10

Scheme I



wherein Ar, R^1 and R^3 are as defined above for Formula I;
 R^{14} , R^{15} and R^{16} are encompassed by the definition of X in
 Formula I;

15

diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these.

10 Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may 15 also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those 25 suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland 30 fixed oil may be employed including synthetic mono-or